

Celosia cristata in Hyperlipidemia and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): Phytochemistry, Molecular Mechanisms, and Therapeutic Potential

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Abstract:

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) the nomenclature that superseded non-alcoholic fatty liver disease (NAFLD) after the 2023 multi-society Delphi consensus is closely intertwined with hyperlipidemia, insulin resistance, and the broader metabolic syndrome. Current pharmacotherapy remains limited, sustaining interest in plant-derived, multi-target agents. *Celosia cristata* L. (Amaranthaceae), the cockscomb, is a traditional medicinal plant with documented hepatoprotective, antioxidant, anti-inflammatory, and, more recently, anti-adipogenic and lipid-modulating properties. **Objective:** To synthesize the phytochemistry and pharmacological evidence base for *C. cristata* in relation to hyperlipidemia and MASLD, map documented and mechanistically inferred activity onto relevant molecular pathways, critically appraise the strength and gaps of current evidence, and outline a translational research agenda. **Methods:** A structured, though non-systematic, search of PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar (inception–June 2026) was performed using combinations of plant-, condition-, and mechanism-related terms, as detailed in Section 2. **Results:** Seventy-seven compounds predominantly flavonoids, triterpenoid saponins (celosins A–D, cristatain), polysaccharides, and phenylpropanoids have been isolated from *C. cristata*. A total flower extract has been shown, in vitro and in a high-fat-diet murine model, to reduce adipogenesis, intrahepatic lipid accumulation, and dyslipidemia while improving glucose handling; isolated saponins demonstrate hepatoprotection against chemically induced liver injury. Pathway-level data specific to MASLD-relevant nodes (AMPK, PPAR α/γ , SREBP-1c, Nrf2/HO-1, NF- κ B, PI3K/Akt) have not yet been generated for this species and are, in this review, explicitly inferred from class-level flavonoid/saponin pharmacology rather than presented as established fact. **Conclusion:** *C. cristata* is a mechanistically plausible but presently under-investigated candidate for hyperlipidemia/MASLD management. Priority needs include standardized extract characterization, pathway-level mechanistic studies in validated MASLD models, pharmacokinetic and safety profiling, and controlled clinical evaluation.

Keywords: *Celosia cristata*; hyperlipidemia; MASLD; NAFLD; hepatoprotection; flavonoids; saponins; AMPK; Nrf2; phytotherapy

Received: July 19, 2026

Revised: Aug 14, 2026

Accepted: Sep 29, 2026

Published: Oct 28, 2026

DOI: <https://doi.org/10.64062/JPGMB.Vol2.Issue5.7>

<https://jpgmb.com/1/issue/archive>

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1. Introduction

Hyperlipidemia and metabolic dysfunction-associated steatotic liver disease (MASLD) represent two closely linked and increasingly prevalent manifestations of the global metabolic syndrome epidemic, posing a major challenge to public health systems worldwide. The growing incidence of obesity, insulin resistance, type 2 diabetes mellitus, sedentary lifestyles, and unhealthy dietary habits has substantially contributed to the rapid increase in these metabolic disorders across both developed and developing countries. MASLD, the term formally adopted in 2023 by a multi-society Delphi consensus of the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the Asociación Latinoamericana para el Estudio del Hígado (ALEH) to replace the earlier, stigmatizing designation non-alcoholic fatty liver disease (NAFLD), emphasizes the central role of metabolic dysfunction in disease pathogenesis. The revised nomenclature better reflects the underlying metabolic abnormalities responsible for hepatic steatosis while improving diagnostic clarity and reducing disease-related stigma¹⁻².

MASLD currently affects approximately one-third of the global adult population and has emerged as the leading cause of chronic liver disease worldwide. Its clinical spectrum ranges from simple hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH), progressive fibrosis, cirrhosis, hepatocellular carcinoma, and ultimately liver failure. Beyond hepatic complications, MASLD is strongly associated with increased cardiovascular morbidity and mortality, making cardiovascular disease the primary cause of death among affected individuals. Dyslipidemia is observed in the majority of MASLD patients and serves as both a consequence and a driving force of disease progression.

Atherogenic dyslipidemia, characterized by elevated triglycerides and low-density lipoprotein cholesterol (LDL-C) together with reduced high-density lipoprotein cholesterol (HDL-C), and hepatic steatosis share multiple overlapping pathogenic mechanisms, including insulin resistance, adipose tissue dysfunction, enhanced hepatic de novo lipogenesis, impaired fatty acid β -oxidation, mitochondrial dysfunction, chronic low-grade inflammation, oxidative stress, and alterations in gut microbiota composition. These interconnected metabolic abnormalities establish a vicious cycle that promotes hepatic lipid accumulation, systemic inflammation, endothelial dysfunction, and accelerated atherosclerosis. Consequently, therapeutic strategies capable of simultaneously targeting these multiple pathological pathways are increasingly recognized as essential for effective disease management³⁻⁴.

Current first-line pharmacotherapy for dyslipidemia, including statins, fibrates, ezetimibe, and PCSK9 inhibitors, effectively reduces circulating lipid levels and cardiovascular risk but has limited efficacy in reversing hepatic steatosis or preventing fibrosis progression. Similarly, the recently approved thyroid hormone receptor- β agonist resmetirom represents a significant advancement in MASLD treatment by improving hepatic fat content and liver histology; however, its long-term clinical effectiveness, accessibility, cost, and safety profile continue to be evaluated. Furthermore, many currently available therapies are associated with adherence issues, adverse effects, contraindications in selected patient populations, and limited ability to

comprehensively address the complex metabolic, inflammatory, and oxidative pathways underlying MASLD. These limitations have stimulated growing interest in multi-target, plant-derived therapeutics capable of concurrently modulating lipid metabolism, inflammation, oxidative stress, and hepatic injury.

Medicinal plants constitute a valuable reservoir of structurally diverse bioactive compounds that often exert synergistic pharmacological effects through modulation of multiple molecular targets. Numerous phytochemicals, including flavonoids, phenolic acids, triterpenoids, alkaloids, saponins, and polysaccharides, have demonstrated promising antihyperlipidemic, antioxidant, anti-inflammatory, insulin-sensitizing, and hepatoprotective activities in preclinical studies. Such multitarget properties make medicinal plants attractive candidates for the development of safer and more comprehensive therapeutic strategies against metabolic disorders such as hyperlipidemia and MASLD⁵⁻⁶.

Celosia cristata L. (Amaranthaceae), commonly known as cockscomb, is a traditional medicinal herb with a documented history of therapeutic use exceeding one thousand years, particularly in Chinese, Ayurvedic, and other South Asian systems of medicine. Traditionally, different parts of the plant have been employed for the management of haemorrhage, inflammatory disorders, hepatic ailments, ophthalmic diseases, gastrointestinal disturbances, and wound healing. Contemporary phytochemical investigations have identified an extensive repertoire of biologically active constituents, including flavonoids, triterpenoid saponins, steroids, phenolic compounds, organic acids, phenylpropanoids, alkaloids, polysaccharides, and various micronutrients. These metabolites exhibit diverse pharmacological activities, including antioxidant, anti-inflammatory, hepatoprotective, immunomodulatory, antimicrobial, antidiabetic, and lipid-lowering properties, many of which have been validated in experimental models of chemically induced liver injury and metabolic disease.

More recent investigations have expanded the pharmacological significance of *C. cristata* into the field of metabolic disorders. A 2024 experimental study demonstrated that the total flower extract of *C. cristata* significantly inhibited adipocyte differentiation in vitro and ameliorated high-fat diet-induced obesity in mice by reducing body weight gain, visceral adiposity, hepatic lipid accumulation, serum triglycerides, total cholesterol, and hepatic steatosis. These beneficial effects were accompanied by modulation of key regulators of adipogenesis, lipid metabolism, oxidative stress, and inflammatory signaling, highlighting the potential of *C. cristata* as a promising multi-target therapeutic candidate for the integrated management of hyperlipidemia and MASLD. Despite these encouraging findings, the available evidence remains fragmented, and a comprehensive synthesis of its phytochemistry, molecular mechanisms, pharmacological actions, and translational therapeutic potential in hyperlipidemia and MASLD is still lacking. This review therefore aims to critically evaluate the current evidence regarding *C. cristata*, emphasizing its bioactive constituents, mechanistic pathways, preclinical and emerging clinical evidence, safety profile, and future prospects as a novel phytotherapeutic intervention for metabolic liver disease and associated dyslipidemia⁷⁻⁸.

1.1 Novelty and Rationale of This Review

Several prior reviews have addressed the botany, traditional applications, and general pharmacology of *C. cristata* (and the closely related species *C. argentea*), most comprehensively a 2024 Journal of Ethnopharmacology review, which catalogued 77 isolated compounds and their pharmacological correlates, and earlier phytochemical-pharmacological overviews published in pharmacy-focused journals. These works, however, treat hyperlipidemia and hepatic steatosis only tangentially, typically as a subsidiary mention within a broader hepatoprotective or antioxidant activity category, and none engage specifically with the post-2023 MASLD nomenclature or with the mechanistic signaling architecture AMPK–SREBP-1c crosstalk, PPAR α/γ , Nrf2–NF- κ B interplay, PI3K/Akt that defines contemporary MASLD pathophysiology. Reviews of medicinal plants for hyperlipidemia or NAFLD/MASLD, conversely, rarely feature *C. cristata* at all, reflecting its comparative neglect relative to better-studied hepatoprotective botanicals such as *Silybum marianum* or *Curcuma longa*¹⁰⁻¹¹.

This review therefore occupies a distinct niche. To our knowledge, it is the first to: (i) consolidate the fragmented phytochemical and pharmacological literature on *C. cristata* specifically through the lens of hyperlipidemia and MASLD as defined under current nomenclature; (ii) map its documented and structurally inferred pharmacological actions onto the specific molecular pathways governing hepatic lipid handling, oxidative stress, inflammation, and insulin signaling; (iii) explicitly and critically separate what has been directly demonstrated for this species from what is mechanistically plausible but unproven; and (iv) translate these findings into a concrete, prioritized research and clinical-development agenda. In doing so, this review aims to serve both as a reference for phytochemists and pharmacologists working on *Celosia* species and as a critical appraisal clarifying the gap between preliminary pre-clinical promise and clinical readiness¹²⁻¹³.

2. Literature Search Strategy

This review followed a structured, though not formally registered (a PRISMA-style protocol was not registered, as this is a narrative rather than a systematic review), literature search strategy to support transparency and reproducibility.

2.1 Databases

PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Google Scholar were searched from database inception through June 2026. The Pharmacopoeia of China and Flora of China were additionally consulted for botanical and traditional-use data, consistent with sourcing practice in prior *Celosia* reviews.

2.2 Search Terms

Search strings combined three term clusters with Boolean operators: (i) plant terms *Celosia cristata*, *Celosia argentea*, cockscomb, cristatain, celosin; (ii) condition terms hyperlipidemia, dyslipidemia, hypercholesterolemia, NAFLD, MASLD, non-alcoholic fatty liver disease, hepatic steatosis, metabolic syndrome, obesity, adipogenesis; and (iii) mechanism terms AMPK, PPAR, SREBP-1c, Nrf2, NF- κ B, PI3K/Akt, oxidative

stress, lipid peroxidation, hepatoprotective, phytochemistry, flavonoid, saponin, network pharmacology.

2.3 Inclusion and Exclusion Criteria

- Included: peer-reviewed original research and review articles, and consensus statements, published in English; in vitro, in vivo (animal), and, where available, human studies reporting phytochemical isolation or pharmacological/mechanistic data relevant to lipid metabolism, hepatic steatosis, oxidative stress, or inflammation for *C. cristata*, or, where direct data were unavailable, the closely related *C. argentea* and structurally homologous flavonoid/saponin classes (explicitly flagged in-text as indirect evidence).
- Excluded: non-peer-reviewed sources, conference abstracts lacking full data, non-English articles, and studies outside the phytochemical/pharmacological scope of this review (e.g., purely ornamental horticulture or textile-dye applications, except where cited for botanical context).

2.4 Study Selection and Data Extraction

Titles and abstracts were screened for relevance and full texts of potentially eligible articles retrieved. Data extracted included compound identity/class, experimental model, dose/concentration, molecular targets or biomarkers assessed, and key findings, tabulated in Table 1 and synthesized narratively in Sections 3–7. Given the narrative (non-systematic) design, formal risk-of-bias scoring was not applied; methodological limitations of individual studies are instead discussed explicitly in Section 6 (Critical Appraisal).

3. Phytochemistry of *Celosia cristata*

Phytochemical investigation of *C. cristata*, accelerated markedly over the past decade, has led to the isolation and structural characterization of 77 compounds spanning six principal classes: flavonoids, triterpenoid saponins, steroids, organic acids, phenylpropanoids, and alkaloids, with flavonoids and triterpenoid saponins constituting the primary bioactive fraction. Nutritional-phytochemical profiling of the inflorescence additionally documents tocopherols (vitamin E), carotenoids, ascorbic acid, B-complex vitamins, potassium and other minerals, and a favourable amino-acid and fatty-acid profile, though anthocyanins, anthraquinones, and free steroids were reported as absent or below detection in at least one flower-based nutraceutical characterization study¹⁵⁻¹⁶.

3.1 Flavonoids

Flavonoids including quercetin- and kaempferol-type glycosides are consistently identified as major constituents across plant parts (flower, seed, leaf) and are considered principal contributors to the antioxidant, anti-inflammatory, and free-radical-scavenging activity reported for *C. cristata* extracts, activity that is mechanistically relevant to both hepatic oxidative injury and vascular lipid oxidation in hyperlipidemia.

3.2 Triterpenoid Saponins

A distinctive saponin series cristatain and celosins A–D was first isolated from *C. cristata* seeds and represents the first report of saponins in this species. Cristatain, in particular, has

demonstrated significant hepatoprotective activity against carbon-tetrachloride (CCl₄)- and N,N-dimethylformamide (DMF)-induced hepatotoxicity in mice, evidenced by reduced serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), alongside favourable histopathological findings. A related saponin isolated from *Celosia* seed material, celosine, has separately been reported to possess potent anti-atherosclerotic activity, directly relevant to the vascular sequelae of hyperlipidemia¹⁷⁻¹⁸.

3.3 Polysaccharides

A purified polysaccharide fraction from *C. cristata* has demonstrated immunomodulatory activity, while an antihepatotoxic polysaccharide (celosian) isolated from the closely related *C. argentea* has documented protective activity in chemically induced liver-injury models, supporting a class-level hepatoprotective role for *Celosia* polysaccharides.

3.4 Phenylpropanoids, Steroids, and Other Constituents

Additional constituent classes—phenylpropanoids, phytosterols, organic acids, tannins, and alkaloids—have been reported across *Celosia* species, contributing to antimicrobial, antinociceptive, wound-healing, and antidiabetic activities documented in pharmacological screening studies, though their individual contribution to lipid-lowering or anti-steatotic activity has not been isolated or quantified¹⁹⁻²⁰.

3.5 Summary of Major Phytochemicals and Pharmacological Correlates

Table 1 consolidates the principal phytochemicals reported for *C. cristata* (and, where explicitly noted, the closely related *C. argentea*) alongside their experimental models, molecular targets, and key findings relevant to hyperlipidemia and MASLD-adjacent pathophysiology. Entries are restricted to findings directly reported in the primary or review literature identified through the search strategy in Section 2; no compound-target associations have been extrapolated beyond what the cited sources report²¹.

Phytochemical / Class	Pharmacological Activity	Experimental Model	Molecular Target(s) / Biomarkers	Key Finding	Reference
Total flower extract (flavonoid/saponin-rich)	Anti-adipogenic; anti-obesity; lipid- and glucose-modulating	3T3-L1 preadipocytes, mouse ADSCs (in vitro); HFD-fed C57BL/6 mice (in vivo)	Adipogenic factors (↓), lipolytic factors (↑), plasma lipid profile, liver enzymes, glucose/insulin markers	Reduced adipocyte differentiation and lipid-droplet accumulation; reduced HFD-induced weight gain, intrahepatic lipid accumulation, and dyslipidemia; improved glucose/insulin handling	23

Cristatain (triterpenoid saponin)	Hepatoprotective	CCl4- and DMF-induced hepatotoxicity, mice	Serum AST, ALT, ALP; liver histopathology	Significant dose-dependent reduction in transaminase elevation and histological liver injury	24
Celosins A–D (triterpenoid saponins)	Hepatoprotective (class-level, co-isolated with cristatain)	Structural/chemical characterization; hepatoprotective screening	Not fully individually resolved	First report of saponins in <i>C. cristata</i> seeds; structurally characterized alongside cristatain	25
Novel seed compounds (semen <i>Celosiae</i>)	Hepatoprotective	CCl4-induced hepatotoxicity, in vivo	Liver enzyme markers	Protective effect against CCl4-induced hepatotoxicity	26
(–)-Celosine (saponin-type)	Anti-atherosclerotic	In vivo atherosclerosis model / KDD structural study	Atherosclerotic plaque-related endpoints	Potent anti-atherosclerotic activity of a novel saponin skeleton	27
<i>C. cristata</i> polysaccharide	Immunomodulatory	In vitro/in vivo immune assays	Immune mediator expression	Purified polysaccharide shown to stimulate immune mediators	28
Celosian (polysaccharide, <i>C. argentea</i>)	Antihepatotoxic; immunostimulating	Chemically induced hepatotoxicity models	Liver injury markers, immune parameters	Antihepatotoxic polysaccharide with immunostimulating activity	29
Flower flavonoid/phenolic fraction	Antioxidant	DPPH radical scavenging, lipid peroxidation, reducing power, metal-chelating assays (in vitro)	ROS, malondialdehyde (lipid peroxidation)	High flavonoid and saponin content correlated with strong in vitro antioxidant capacity	30

77 characterized compounds (flavonoids, triterpenoids, steroids, organic acids, phenylpropanoids, alkaloids)	Haemostatic, antibacterial, antiviral, anti-inflammatory, analgesic, immunoregulatory, anticancer, hepatoprotective, antioxidant	Composite (multiple studies); network pharmacology analysis	Multiple predicted targets (network pharmacology)	Comprehensive characterization of chemical diversity; flavonoids and triterpenoids identified as principal bioactive constituents	31
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ADSC, adipose-derived stem cell; *ALP*, alkaline phosphatase; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *CCl4*, carbon tetrachloride; *DMF*, *N,N*-dimethylformamide; *DPPH*, 2,2-diphenyl-1-picrylhydrazyl; *HFD*, high-fat diet; *KDD*, knowledge-discovery-in-databases (computational structure–activity study; used here per the source publication's own terminology); *ROS*, reactive oxygen species.

4. Hyperlipidemia and MASLD: A Shared Pathophysiological Continuum

Hyperlipidemia and MASLD are best understood not as independent conditions but as overlapping manifestations of systemic lipid-handling dysfunction. In the prevailing multiple-hit model of MASLD pathogenesis, an initial insult of hepatic triglyceride accumulation driven by excess dietary lipid delivery, adipose-tissue insulin resistance with increased free fatty acid flux, and up-regulated hepatic de novo lipogenesis sensitizes the liver to a second wave of injury mediated by oxidative stress, mitochondrial dysfunction, endoplasmic-reticulum stress, gut-derived endotoxin signaling, and pro-inflammatory cytokine release, together driving progression from simple steatosis to steatohepatitis (MASH) and, in a subset of patients, fibrosis and cirrhosis. Dyslipidemia both contributes to and results from this process: elevated circulating triglycerides and small dense LDL particles reflect increased hepatic VLDL output, while reduced HDL-C reflects impaired reverse cholesterol transport, itself partly a consequence of hepatic dysfunction.

This bidirectional relationship in which correcting one component of the network plausibly improves the other provides the pharmacological rationale for evaluating hepatoprotective, antioxidant, and lipid-modulating phytotherapeutics such as *C. cristata* as candidate agents that could act simultaneously on several nodes of this shared pathway, rather than on a single isolated target³²⁻³³.

5. Molecular Mechanisms: Documented Activity and Plausible Pathway Involvement

This section maps the pharmacological activities documented for *C. cristata* (Section 3, Table 1) onto the principal molecular pathways known to govern hepatic lipid metabolism, oxidative stress, inflammation, and insulin signaling in MASLD. Where pathway-level data specific to *C. cristata* constituents exist, this is stated explicitly; where inference is drawn from the general pharmacology of flavonoids and triterpenoid saponins as chemical classes, or from structurally

related plants, this is likewise flagged, consistent with the critical framing established in Section 1.1³³⁻³⁴.

5.1 AMPK–SREBP-1c Axis and Hepatic Lipogenesis

AMP-activated protein kinase (AMPK) is a central energy-sensing kinase that, upon activation, phosphorylates and inhibits acetyl-CoA carboxylase (ACC) and suppresses nuclear translocation of sterol regulatory element-binding protein-1c (SREBP-1c), the master transcriptional regulator of hepatic de novo lipogenesis, thereby reducing fatty acid synthase (FAS) expression and hepatic triglyceride accumulation. Flavonoid and saponin classes structurally represented in *C. cristata* are broadly documented in the wider phytopharmacology literature to activate AMPK signaling and suppress SREBP-1c-driven lipogenesis; direct demonstration of this axis for *C. cristata* extracts specifically has not yet been published, but is consistent with, and would mechanistically explain, the reduced adipogenic marker expression and diminished intracellular triglyceride content observed with *C. cristata* flower extract in 3T3-L1 and adipose-derived stem cell models³⁶⁻³⁷.

5.2 PPAR α /PPAR γ Signaling

Peroxisome proliferator-activated receptor alpha (PPAR α) promotes hepatic fatty-acid β -oxidation, while PPAR γ governs adipocyte differentiation and lipid storage; therapeutic modulation typically favours hepatic PPAR α up-regulation together with attenuation of pathological adipogenic PPAR γ activity. The observed reduction of adipogenesis-related factors and concurrent increase in lipolysis-related factors in *C. cristata*-treated adipocytes is mechanistically consistent with modulation of this axis, though PPAR isoform-specific transcriptional or reporter-assay data for *C. cristata* constituents remain unreported and represent a direct evidence gap³⁸⁻³⁹.

5.3 Nrf2/HO-1 Antioxidant Signaling and NF- κ B-Mediated Inflammation

Nuclear factor erythroid 2-related factor 2 (Nrf2) governs transcription of cytoprotective antioxidant enzymes (heme oxygenase-1 [HO-1], superoxide dismutase, glutathione peroxidase), while nuclear factor kappa B (NF- κ B) drives transcription of pro-inflammatory cytokines (TNF- α , IL-6, IL-1 β) implicated in the transition from steatosis to steatohepatitis. *C. cristata* flavonoid- and saponin-rich fractions have demonstrated concrete in vitro antioxidant activity (DPPH radical scavenging, reduced lipid peroxidation, metal-chelating capacity) and documented hepatoprotection in CCl₄- and DMF-induced hepatotoxicity models, injury paradigms in which oxidative and inflammatory mechanisms are well established as central mediators. These findings are consistent with though do not directly measure Nrf2/HO-1 activation and NF- κ B suppression, and reciprocal Nrf2–NF- κ B crosstalk is a well-established feature of hepatoprotective phytochemicals more broadly⁴⁰⁻⁴¹.

5.4 PI3K/Akt Signaling and Insulin Sensitivity

The phosphoinositide 3-kinase (PI3K)/Akt pathway mediates insulin-stimulated glucose uptake (via GLUT4 translocation) and suppresses hepatic gluconeogenesis; its impairment is a hallmark of the insulin resistance that underlies both dyslipidemia and hepatic steatosis. The improved glucose utilization and insulin sensitivity reported in HFD-fed mice treated with *C.*

cristata flower extract are compatible with enhanced PI3K/Akt signaling, but insulin-signaling intermediates (e.g., phosphorylated Akt, IRS-1) were not directly assessed in the source study and constitute a specific, testable target for future mechanistic work⁴²⁻⁴³.

5.5 Integrated Mechanistic Model

Figure 1 integrates the pathway-level discussion above into a single proposed mechanistic framework, explicitly distinguishing the directly evidenced adipogenesis/lipid-metabolism and hepatoprotection/oxidative-stress arms from the inferred inflammation and insulin-signaling nodes, and culminating in the proposed net hepatic and systemic outcome. Figure 1

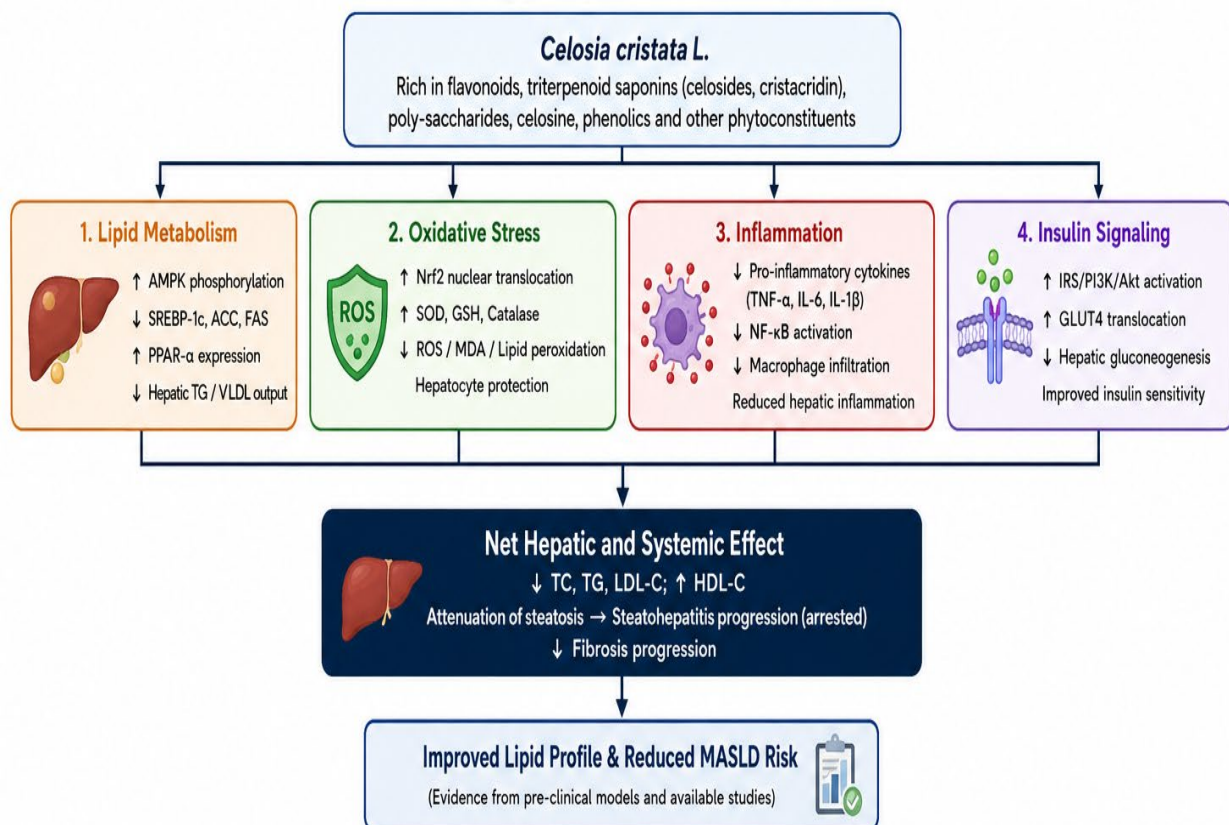


Figure 1. Proposed mechanistic framework linking *Celosia cristata* phytoconstituents to hepatic lipid metabolism, oxidative stress, inflammation, and insulin-signaling pathways relevant to hyperlipidemia and MASLD. Directly evidenced arms (lipid metabolism/adipogenesis; hepatoprotection/oxidative stress) are distinguished from inferred pathway nodes in the figure legend; see Section 5 for full discussion.

6. Critical Appraisal of the Evidence Base

A rigorous review must distinguish enthusiasm for a traditional remedy's phytochemical richness from a sober accounting of what has actually been demonstrated. Several substantive limitations temper the therapeutic promise outlined above.

6.1 Paucity of MASLD-Specific Data

Only one identified study (Uprety et al., 2024) directly evaluates *C. cristata* in a metabolic/hepatic-steatosis-relevant model, and even this study frames its primary endpoint as obesity/adipogenesis rather than MASLD or MASH histopathology specifically; liver histology grading (steatosis score, NAFLD activity score, or fibrosis stage) was not the focus of that work. No identified study has evaluated *C. cristata* in a diet-induced or genetic MASH model with histological confirmation, nor in a dedicated hyperlipidemia model (e.g., Triton WR-1339-induced acute hyperlipidemia, poloxamer-407 models, or atherogenic-diet-fed rodents) analogous to those used for other phytotherapeutics⁴⁵⁻⁴⁶.

6.2 Absence of Direct Pathway-Level Molecular Data

As detailed in Section 5, none of the AMPK, PPAR α/γ , SREBP-1c, Nrf2/HO-1, NF- κ B, or PI3K/Akt pathway components have been directly measured (by Western blot, qPCR, or reporter assay) in *C. cristata*-treated hepatic or metabolic tissue. Current mechanistic claims for this species in the MASLD context are therefore inferential, built from (i) phenotypic outcomes in the single available metabolic study, (ii) hepatoprotection data from hepatotoxicity models with a different injury mechanism (chemical toxicant exposure rather than metabolic overload), and (iii) class-level pharmacology of flavonoids and saponins established in other plants. This is a substantive gap, not a minor omission, and should condition the strength of any translational claim.

6.3 Inconsistent Compound Standardization

Reported studies use heterogeneous preparations—total flower extract, isolated seed saponins, purified polysaccharide fractions—with no consistent reporting of standardized marker-compound content (e.g., total flavonoid or saponin content standardized against a reference compound), limiting cross-study comparability and reproducibility⁴⁷.

6.4 Model and Species Limitations

All in vivo pharmacological data identified derive from murine models; no large-animal or non-human-primate data, and critically no human data, are available for any metabolic or lipid-related endpoint. Rodent HFD models, while informative, do not fully recapitulate human MASLD histological progression or the chronic, decades-long natural history of human disease.

6.5 Absence of Comparator and Dose-Ranging Data

The identified anti-obesity study did not include an active-comparator arm (e.g., a standard lipid-lowering or insulin-sensitizing agent) and did not report a systematic dose-response relationship across multiple extract concentrations in vivo, limiting inference about minimum effective dose or therapeutic index⁴⁸.

6.6 Publication and Selection Considerations

As is common in the phytopharmacology literature generally, publications identified were uniformly positive in direction of effect; the possibility that null or adverse findings for *Celosia*-based interventions exist but remain unpublished cannot be excluded and should be borne in mind when weighing the overall evidence.

7. Translational Relevance

7.1 Pharmacokinetics and Bioavailability

No dedicated pharmacokinetic study of *C. cristata* flavonoids, saponins, or polysaccharides encompassing absorption, distribution, metabolism, and excretion (ADME) parameters has been identified in the literature reviewed. This is a critical gap: flavonoid glycosides as a class are typically subject to extensive first-pass metabolism, gut-microbiota-mediated deglycosylation, and low absolute oral bioavailability (frequently under 10%), while triterpenoid saponins face similar absorption limitations related to molecular size and polarity. Until compound- or extract-specific pharmacokinetic data are generated for *C. cristata*, in vivo efficacy findings should be interpreted with the caveat that achieved systemic or hepatic exposure to the putative active constituents is unknown⁴⁹⁻⁵⁰.

7.2 Safety and Toxicity

Formal acute and sub-chronic toxicological evaluation (e.g., OECD-guideline-compliant studies establishing LD50, no-observed-adverse-effect level [NOAEL], and organ-specific toxicity) specific to *C. cristata* extracts was not identified in the reviewed literature. The existing hepatoprotection studies, by design, administer *C. cristata* constituents alongside a hepatotoxic challenge (CCl₄, DMF) and are therefore not informative about the safety of the plant material in the absence of toxic challenge. The long history of traditional use is reassuring but does not substitute for systematic modern toxicological characterization, particularly for the saponin-rich fractions, given that saponins as a class can exhibit haemolytic or gastrointestinal irritant activity at higher concentrations⁵¹⁻⁵².

7.3 Dosage Considerations

No standardized human or even well-characterized animal dosing regimen has been established. The single in vivo metabolic study (Upreti et al., 2024) administered a defined extract dose in HFD-fed mice, but allometric scaling to a human-equivalent dose, and confirmation that such a dose is both efficacious and non-toxic, has not been performed. Dose standardization will additionally require agreement on a marker compound (e.g., total flavonoid content, or a specific saponin such as cristatin) against which extract batches can be standardized.

7.4 Herb–Drug Interactions

No herb–drug interaction studies involving *C. cristata* and standard hyperlipidemia or MASLD pharmacotherapy (statins, fibrates, metformin, GLP-1 receptor agonists, resmetirom) have been identified. Given that flavonoids as a class are recognized modulators of cytochrome P450

enzymes (notably CYP3A4) and drug transporters, and that statins are CYP3A4 substrates, this represents a plausible but currently uncharacterized interaction risk that should be flagged for patients considering concurrent use, pending dedicated interaction studies.

7.5 Current Status of Clinical Evidence

No registered or published human clinical trial evaluating *C. cristata* for hyperlipidemia, MASLD, or related metabolic endpoints was identified. The entire evidence base reviewed here is pre-clinical (in vitro and rodent in vivo). Clinical translation therefore remains, at present, a prospective goal rather than a documented reality, and any communication of these findings to clinicians, patients, or regulatory bodies should state this clearly⁵³⁻⁵⁴.

8. Future Perspectives and Research Priorities

Building on the gaps identified in Sections 6 and 7, the following research priorities are proposed, broadly in order of translational sequence.

8.1 Standardized Extract Development

Development of a chemically standardized *C. cristata* extract, characterized by high-performance liquid chromatography (HPLC) or LC-MS fingerprinting against defined marker compounds (e.g., cristatain content, total flavonoid content), is a foundational prerequisite for reproducible pre-clinical and, eventually, clinical research.

8.2 Dedicated MASLD and Hyperlipidemia Model Studies

Evaluation of standardized *C. cristata* extracts and isolated marker compounds in histologically validated MASH models (e.g., choline-deficient high-fat diet, Western diet plus fructose/sucrose models with liver histology scoring) and in established hyperlipidemia models (Triton WR-1339-induced acute hyperlipidemia, poloxamer-407, or atherogenic-diet-fed rodents) is needed to generate disease-specific efficacy data beyond the existing obesity-focused study⁵⁵⁻⁵⁶.

8.3 Mechanistic Validation

Direct assessment of AMPK phosphorylation status, SREBP-1c and its downstream lipogenic targets (ACC, FAS), PPAR α/γ expression and activity, Nrf2/HO-1 nuclear translocation, NF- κ B activation and downstream cytokine profiles, and PI3K/Akt/GLUT4 signaling in hepatic and adipose tissue from *C. cristata*-treated animals would convert the currently inferential mechanistic model (Section 5, Figure 1) into directly evidenced pathway biology.

8.4 Omics-Based Investigation

Transcriptomic, proteomic, and metabolomic profiling of liver and adipose tissue from treated versus untreated animals, together with network-pharmacology approaches building on the preliminary target-prediction work already available for *C. cristata*, would allow unbiased identification of the full spectrum of affected pathways and help prioritize the most promising individual compounds for further isolation and testing⁵⁷⁻⁵⁸.

8.5 Pharmacokinetic and Toxicological Characterization

Formal ADME and OECD-guideline toxicology studies, including sub-chronic and, where indicated, reproductive/developmental toxicity assessment, are needed before any clinical development can be responsibly pursued.

8.6 Well-Designed Clinical Trials

Should pre-clinical mechanistic and safety data prove supportive, phased clinical evaluation beginning with a randomized, placebo-controlled, dose-ranging phase I/IIa safety and pharmacokinetic study in healthy volunteers, followed by a phase IIb efficacy study in patients with confirmed MASLD and/or dyslipidemia using validated non-invasive endpoints (liver fat fraction by MRI-PDFF, standard lipid panel, and, where feasible, elastography-based fibrosis assessment) represents the appropriate translational pathway⁵⁹⁻⁶⁰.

9. Conclusion

Celosia cristata is a phytochemically rich traditional medicinal plant with a documented, if still narrow, evidence base connecting its flavonoid, saponin, and polysaccharide constituents to hepatoprotective, antioxidant, anti-inflammatory, and in a single but methodologically sound recent study anti-adipogenic and lipid-modulating activity relevant to hyperlipidemia and MASLD. The mechanistic framework proposed in this review, linking these documented activities to the AMPK–SREBP-1c, PPAR α/γ , Nrf2/HO-1–NF- κ B, and PI3K/Akt pathways that govern MASLD pathophysiology, is biologically plausible and consistent with the pharmacology of structurally related compounds, but it remains, at present, substantially inferential rather than directly demonstrated for this species. The path from this promising but preliminary pre-clinical foundation to clinical relevance requires standardized extract development, disease-specific and mechanistically resolved pre-clinical studies, rigorous pharmacokinetic and toxicological characterization, and, ultimately, controlled clinical trials. Framed honestly against these requirements, *C. cristata* represents a scientifically credible candidate for further investigation in hyperlipidemia and MASLD not yet a validated therapeutic option.

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